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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,371	03/22/2001	Graham McCreath	8117-14	4297

23973 7590 04/19/2006

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EXAMINER	
HANLEY, SUSAN MARIE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,371	MCCREATH ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,9 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,9 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendment filed 12/27/05 are acknowledged.

Claims 1, 3, 5, 9 and 12-14 are pending.

Response to Arguments

Applicant's arguments with respect to claims 1, 3, 5, 9 and 12-14 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 5, 9 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lord (US 6,037,457) in view of Wilkins et al. (1992; "Wilkins"), Blomback et al. (1966; "Blomback"), Vukovich et al. (1980, abstract ; "Vukovich"), Tripodi (WO 9213495), Garner et al. (US 5,639,940 ; "Garner"), Jennissen et al. (English translation of DE 4240119; "Jennissen"), Kutzko et al. (US 6,268,847; "Kutzko"), Sasaki et al. (US 4,295,855; "Sasaki") and Clark et al. (US 5,935,850: "Clark").

Lord discloses a method for producing, concentrating and purifying recombinant fibrinogen (rFIB) from mammalian cell culture. The rFIB is concentrated from the cell culture media by precipitation with ammonium sulfate and then purifying the concentrated rFIB by any type of chromatography including HIC chromatography (column 6, lines 36-52). Lord teaches that both the concentration step and the purifying step are carried out in the presence of one or more protease inhibitors such as epsilon-aminocaproic acid (col. 8, lines 18-21 and 29).

Lord does not teach the application of the disclosed isolation processes are applied to isolating fibrinogen from milk, wherein fibrinogen is precipitated of rFib from milk, separated from the precipitated rFib from whey proteases to recover part-purified fibrinogen having high and low molecular

weight sub-fraction and contacting and eluting the part-purified fibrinogen with HIC resin to produce sub-fraction of fibrinogens having high A alpha-chain integrity.

Wilkins discusses the isolation of recombinant proteins from milk. Wilkins discloses that the degree of difficulty in isolating recombinant protein is related to the concentration of the protein in milk. The colloidal nature of milk adds a degree of complexity in that fat must be removed and casein micelles precipitated. The precipitation method is useful if the recombinant protein partitions into the casein precipitate or the whey. Once the protein is obtained from the whey or casein precipitate, it is subjected to classical chromatographic procedures (p. 336, right column, 1st full paragraph). Wilkins also teaches that milk contains serine proteases such as plasmin which is bound predominantly to the casein micelles. Milk proteases can degrade the desired recombinant protein (p. 335, left column, "Proteases in Milk").

Blomback discloses amides can be used to fractionally precipitate proteins from plasma or milk. Dimethylformamide (DMFA) was added to blood plasma at neutral pH to obtain a fibrinogen precipitate. Blomback states that the disclosed amide reagents can be used to fractionate proteins in milk with "equal success" (p. 2317, top of right column).

Tripodi discloses precipitating fibrinogen from plasma with PEG in buffer containing epsilon-aminocaproic acid. The buffer system is said to be important because it prevents premature conversion of fibrinogen into fibrin (page 8, line 34 to page 9, line 21).

Vukovich et al. (1980) teach that fibrinogen can be highly purified from plasma using HIC with for example, butyl-sepharose.

The combined disclosures by Lord, Blomback, Wilkins, Tripodi and Vukovich demonstrates that the precipitation of fibrinogen from mammalian cell culture, plasma or milk using fractional precipitation and chromatography was known at the time of the invention. Thus, the same precipitation and chromatography strategy for purifying fibrinogen from diverse sources it the same. Wilkins discloses that subsequent chromatography steps are accomplished with standard methods that are the same as

those used for purification of proteins from plasma. Further, the ordinary artisan would have known that recombinant protein could be partitioned to the casein fraction.

Garner discloses that recombinant fibrinogen can be recovered from milk by using standard practices such as skimming, precipitation, filtration and protein chromatography techniques. Garner et al. state that it is preferred to produce fibrinogen having a ratio of Aα : Bβ : γ expression units having a ratio in the range of 0.5-1:0.5-1:0.5-1 (col. 7, lines 15-20). This preferred ratio corresponds to the limitation of high Aα-chain integrity recited in instant claim 1 because degradation of the Aα chain leads to an alteration in the preferred chain ratio which represents intact fibrinogen. The milk can be derived from a sheep, goat, pig or cattle (col. 8, lines 64-68). The source of the fibrinogen is human (see the sequence listing).

Jennissen discloses the purification of human fibrinogen in a single chromatographic step by applying plasma to a hydrophobic interaction column comprising pentyl-Sepharose. The protein was eluted using a gradient buffer. Figure 1 demonstrates that the purified fibrinogen was separated into sub-fractions. The purified fibrinogen was molecularly uniform and fully active. The purified human fibrinogen was subjected to SDS gel electrophoresis to characterize the individual chains of the purified fibrinogen. The molecular weight of the human Aα-chain was 72 kDa (col. 5, lines 20-55). This is the molecular weight of the native Aα-chain. Thus, the purified fibrinogen is undegraded and intact. Thus, Jennissen et al. demonstrate that HIC chromatography for the purification of fibrinogen is one of the many known purification methods for fibrinogen.

Kutzko teaches that fibrinogen can be separated from milk and purified by any number of chromatographic techniques including HIC (col. 3, lines 55-57). The protein can be fibrinogen (claim 5).

Thus, Lord, Vukovich, Tripodi, Kutzko and Jennissen all teach either generically or specifically that HIC resin is suitable for the reliable to produce sub-fractions having fibrinogen with high Aα-chain chain integrity from cell culture, milk or plasma.

Sasaki discloses that it is known that analogs of lysine precipitate fibrinogen from plasma. These analogs include glycine and epsilon-aminocaproic acid (col. 2, lines 33-37).

Clark teaches that epsilon-aminocaproic acid interacts with the active site of plasmin and prevents its association with tissue plasminogen activator (col. 17, lines 32-35).

It would have been obvious to one of ordinary skill in the art at the time to apply the isolation strategy similar to that of Lord to isolate recombinant fibrinogen from milk by precipitating rFib from milk, separating the precipitated rFib from whey proteases to recover part-purified fibrinogen having high and low molecular weight sub-fraction and contacting and eluting the part-purified fibrinogen with HIC resin to produce sub-fraction of fibrinogen having high A alpha-chain integrity. The ordinary artisan would have been motivated to do this because the disclosures by Lord, Blomback, Wilkins, Tripodi and Vukovich show that the isolation strategy for protein from plasma are equally applicable to the isolation of the same protein from milk. The ordinary artisan would have realized from Wilkins and Blomback that one could reasonably expect that the isolation method for the protein from plasma could be applied to the isolation from the same protein from milk. Blomback asserts that the precipitation of fibrinogen by DMFA will work equally well for milk proteins. Thus, the ordinary artisan would have had a reasonable expectation that fibrinogen could be fractionally precipitated from milk in the presence of a lysine analog that inhibits serine proteases (the first step of Lord) and then applying the precipitate to a chromatography resin (the second step of Lord) because this strategy was successful for Lord.

The ordinary artisan would have been motivated to employ a HIC resin because Garner teaches that any chromatographic method is acceptable and the prior art discloses that HIC chromatography is

generically suitable for isolating fibrinogen from plasma or cell culture and specifically by Jennissen who employs HIC chromatography in a single purification step for fibrinogen from plasma. Thus, the ordinary artisan would have had a reasonable expectation that a fibrinogen milk precipitate could be purified on HIC resin because said purification is successful for fibrinogen obtained from plasma.

The ordinary artisan would have been motivated to employ a protease inhibitor such as epsilon-aminocaproic acid during the precipitation step because milk, like plasma, contains serine proteases that will degrade the desired product (Wilkins taught that milk contains plasmin). The ordinary artisan would have been further motivated because lysine analogs cause fibrinogen to precipitate in plasma (Sasaki) and it is known epsilon-aminocaproic acid prevents plasmin from associating with its protein substrate (Clark). The ordinary artisan would have had a reasonable expectation that a protease inhibitor such as epsilon-aminocaproic acid could inhibit milk plasmin and aid the precipitation of the fibrinogen because said protease inhibitors have been shown by Lord, Sasaki and Clark to exert these effects.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Hanley
Patent Examiner
1651

JEAN C. WITZ
PRIMARY EXAMINER